

comprising a pore-forming agent. Basis for this claim appears in the specification, for example on page 3, line 19 through page 4, line 10.

**Rejection Under 35 USC §112**

Claims 1-7 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. The Examiner contends that it is not clear what the terms "derivative" and "pore forming agent" mean, even to one skilled in the art.

It is well known in the chemical arts that "derivative" refers to a substance related to another substance by modification or partial substitution. In addition, it is submitted that the meaning of the term "derivative" is clear based on the specification. It is set forth on page 6, lines 15-22, and page 7, lines 1-10 of the specification that hyaluronic acid derivatives are prepared by hydration of insoluble or partially soluble starting materials of hyaluronic acid non-woven pads or sponges. Details describing the hyaluronic starting materials and preparation of injectable hyaluronic formulations are set forth on page 7 lines 11-27. At page 3, line 22, it is stated that the injectable formulations are prepared by transforming non-woven pads and sponges of hyaluronic acid benzyl esters by hydration or solvent addition. Applicants submit therefore that claims 1-7 are not indefinite based on the term "derivative."

It is submitted that the term "pore-forming agent" is amply defined in the specification and its meaning clear, especially for one skilled in the art. As set forth in the specification at page 4, line 2 through 14, a pore former may be introduced to increase porosity. It is disclosed that the pore formers allow in situ pore formation after injection of the osteogenic formulation in vivo. Suitable liquid pore formers are disclosed such as polyethylene glycol and solid pore formers such as sodium bicarbonate, sodium chloride citric acid, and sucrose. The pores leave voids sufficient for cell ingrowth. The formation of bone within pores is described in Example 3, page 10 lines, 13-14. One skilled in the art of pharmaceutical osteoinductive formulations would not therefore, as suggested by the Examiner, consider a drill bit as a pore-forming agent. Applicants submit that the claims are not indefinite based on the term "pore forming agent."

**Rejections Under 35 USC §102**

Claims 1, 2, 4 and 7 are rejected as anticipated by Kubler et al., cited for allegedly disclosing a mixture comprising calcium phosphate, hyaluronic acid and BMP. The Examiner states that a mixture is a formable paste that is injectable much like icing through a pastry bag or caulk through a caulk gun. Kubler et al. refer to the preparation of ossifying material suitable for bone implants. The present invention is directed to

pharmaceutical compositions injectable, for instance, in a patient in need of bone or cartilage formation or repair. Furthermore, the Kubler et al. preparation contains calcium phosphate and/or calcium fluorophosphate particles mixed with atelocollagen. This composition can contain huyaluronic acid, BMP, and adjuvants. Applicants have discovered that tricalcium phosphate (TCP) in the formulation increases retention of BMP at the site of injection thereby accelerating fracture repair. Applicants claim an injectable composition comprising the osteogenic protein and the hyaluronic acid and therefore, the claims are is not anticipated by Kubler et al.

### **Rejections Under 35 USC 103**

Claims 1-7 are rejected as allegedly unpatenable over Wozney et al. (U.S. Patent No. 6,187,742). The Examiner contends that although there is no explicit exemplification of the combination of the elements of Applicants' claimed invention, it would have been obvious to one of ordinary skill in the art to choose from the list provided in the cited reference for each category of substances as described in the cited reference. Applicants submit that the presently claimed invention is not obvious over Wozney et al. Wozney et al., is directed to a method for regeneration of a functional attachment between ligament and bone comprising administering BMP. Numerous materials, which may be useful as carriers, are described such as collagenous materials

and porous particulate polymers. In addition, sequestering agents are disclosed such as cellulosic material, hyaluronic acids, and sodium alginate among a list of many others - with the preferred agent being carboxymethyl cellulose. Further suitable carriers include hyaluronic acid, surgical mesh sutures and demineralized bone. Several modes of administration are disclosed such as application with a brush or injection.

The presently claimed injectable composition comprising BMP and hyaluronic acid derivatives is neither taught nor suggested by Wozney et al. As the Examiner states, Applicants' claimed invention is not exemplified and Applicants submit that it not obvious based on Wozney et al., to find and select the individual elements of Applicants invention within the lists of many suitable carriers, sequestering agents, and modes of administration set forth in Wozney et al.

Claims 1, 2, 4-7 are rejected as unpatentable over Rhee et al. (U.S. Patent No. 5,752,974) cited for disclosing the combination of BMP-2 or BMP-7, PEG, a cross linked hyaluronic acid or hyaluronic acid, and tricalcium phosphate designed for injection. Although there is no explicit exemplification of the combination of the claimed elements of the present application, the Examiner contends that it would be obvious to one of ordinary skill in the art to choose from the list provided in the cited reference for each of the category of substances as described in the cited reference. Rhee et al. is directed

to methods for completely or partially blocking, augmenting sealing or filling various biological lumens and voids within the body of a patient. The disclosure cited by the Examiner at column 5, lines 51-55 is directed to cross linking hyaluronic acid and collagen together using a synthetic hydrophilic polymer. Tricalcium phosphate is disclosed at column 6 lines 49-57 as part of a composition comprising collagen. Applicants submit that Rhee et al. does not disclose Applicants' claimed invention comprising osteogenic protein and hyaluronic acid for injectable delivery useful for the formation of cartilage and/or bone and repair of tissue damage and fractures, nor the additional TCP component for increasing retention of the osteoinductive protein. It is submitted therefore that Applicants invention is not obvious to one skilled in the art based on the list of substances found in Rhee et al.

Claims 1-5 and 7 are rejected as unpatentable over Valentini et al. (U.S. Patent No. 5,939,323) cited for allegedly disclosing the combination of esterified hyaluronic acid, NaCl and BMP. The Examiner contends that these can be solutions mixed prior to the formation of the scaffold with bioactive molecules including BMPs. The Examiner states that solutions are injectable compositions. The Examiner finds no explicit exemplification of the claimed elements though contends it would have been obvious to one skilled in the art to choose from the list provided. The Valentini et al. disclosure, however is directed to scaffolds for implantation. Valentini et al. do not teach or suggest

Applicants' claimed discovery of an injectable formulation for delivery of osteogenic protein nor the addition of TCP for retention of the osteogenic protein thereby accelerating fracture repair.

**CONCLUSION**


In view of the foregoing remarks, Applicant respectfully request reconsideration of the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

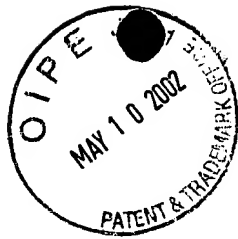
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Date: May 10, 2002

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**Appendix of Amended Claims**

**TECH CENTER 1600/2900**

Claim 1 has been amended as follows:

1. (Amended) A composition for injectable delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising
  - (a) an osteogenic protein; and
  - (b) an injectable hyaluronic acid derivative[s].

The following claim has been added:

11. The composition of claim 2 further comprising a pore-forming agent.

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